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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/708,635	09/22/2000	Kendall A. Smith	2650/1F918-US1	2206

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EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 08/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/708,635	SMITH, KENDALL A.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-8,10 and 15-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-8,10 and 15-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Office Action

Status of the Claims

Acknowledgement is hereby made of receipt and entry of the response filed 28 April, 2004. Claims 1, 5-8, 10, and 15-26 are currently under examination.

35 U.S.C. § 112, Second Paragraph

The previous rejection of claims 1-12, 15, and 16 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is hereby withdrawn in response to applicant's amendment.

35 U.S.C. § 103(a)

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

The previous rejection of claims 1-4, 8-10, 15, and 16 under 35 U.S.C. § 103(a) as being unpatentable over Lane *et al.* (2001) in view of Vandamme *et al.* (1998), is hereby withdrawn in response to applicant's amendment and arguments.

The previous rejection of claims 1, 5-8, 10, 17, under 35 U.S.C. § 103(a) as being unpatentable over Tilg *et al.* (1993) in view of Tsai and Huang (1997), is hereby withdrawn in response to applicant's arguments and amendment.

Non-statutory Double Patenting

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 U.S.P.Q. 644 (C.C.P.A. 1969); *In re Vogel,* 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970); *In re Van Ornum,* 686 F.2d 937, 214 U.S.P.Q. 761 (C.C.P.A. 1982); *In re Longi,* 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985); and *In re Goodman,* 29 U.S.P.Q.2d 2010 (Fed. Cir. 1993). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

The previous rejection of claims 1, 5-8, 10, 15, and 16 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-57 of U.S. Patent No. 6,509,313 in view of Vandamme *et al.* (1998), is hereby withdrawn in response to applicant's argument and amendment.

The previous rejection of claims 1, 5-8, 10, 15, and 16 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-60 of U.S. Patent No. 6,045,788, is hereby withdrawn in response to applicant's arguments and amendment.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5-8, 10, 15-17, and 19-26 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The claims are directed toward methods for enhancing the ability of the immune system to mount an effective immune response after the discontinuation of treatment for an infectious disease through the administration of low-dose IL-2 therapy in such a manner that Grade I toxicity, or higher, is not elicited. The disclosure supports claims that are directed toward methods involving the administration of low-dose IL-2 to HIV-1-infected patients who have received **HAART** and currently have **undetectable levels of plasma HIV-1** (see Example 2, p. 32-40). However, the disclosure does not support the full breadth of the claim language as it is directed toward any infectious disease, any treatment regimen, and any viral load.

The legal considerations that govern enablement determinations

pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to demonstrate that low-dose IL-2 administration is effective at generating useful immune responses in patients who have measurable viral loads. The claims do not address the level of virus present in any given patient who is coming off of a treatment for the infectious disease. The treatment may or may not have been effective at reducing the viral burden. It has been well-documented that HIV-1 produces large quantities of virus. Thus, it is not readily manifest that low-dose IL-2 administration would display any meaningful effects in patients who have measurable viral loads. This is not surprising, since most patients generate robust immune responses that fail to control the virus.

2) The disclosure fails to demonstrate that low-dose IL-2 administration is capable of generating the type of immune responses currently claimed. The prior art (see item 3, below) suggests that often high and toxic doses of IL-2 are required to achieve meaningful immunological responses. Low-dose administration in many situations failed to generate any meaningful

immune or antiviral responses. The disclosure fails to provide sufficient guidance pertaining to this subject.

3) The prior art teaches that the administration of low-dose cytokines is unpredictable and often fails to have any meaningful clinical, immunological, or antiviral effects (Kakumu et al., 1988; Tilg et al., 1993; Pardo et al, 1997). For instance, Kakumu and colleagues (1988) reported that IL-2 administration for the treatment of HBV infection failed to significantly alter serum HBeAg levels, indicating that viral infection was not impaired to any meaningful extent. The authors also reported that IL-2 administration has no meaningful effect on CD4 or CD8 cell numbers. Tilg and colleagues (1993) noted that low-dose IL-2 administration also had no antiviral effects on HBV. Efficient antiviral responses were only noted at higher and more toxic levels. Finally, Pardo and associates (1997) also reported that low-dose IL-2 administration has no significant antiviral effect on HCV replication. Thus, the skilled artisan would readily question the ability of low-dose IL-2 administration to achieve the desired result.

4) The claims are of considerable breadth and are directed toward any virus, dose, and treatment. The claims encompass a large and diverse genus of genotypically/phenotypically unrelated viruses with disparate tropisms and replicative strategies. Thus, it is not readily manifest that the results of any given study can be directly extrapolated to every and all viruses. The prior art suggests the dosage may be critical in each case. It also suggests that the correct dosage may have to be determined empirically. Finally, the disclosure fails to address the breadth of the claim language as it applies to treatment regimens and viral loads. There is no requirement in the claim language that the patient have low levels of virus or that the treatment they are discontinuing has been successful. As noted above, it does not appear that the

IL-2 administration will be effective at controlling or eradicating viral replication when large quantities of the virus are present. **5) The disclosure fails to provide a sufficient number of working embodiments.** The only example discussed in the specification involved HIV-1-infected patients who had just successfully completed a HAART treatment regimen and who currently had no measurable virus. However, the disclosure does not provide any examples involving patients with measurable viral loads from HIV or other viruses. Some preliminary evidence was provided from an HCV study, however, the details of the study and results are vague and indefinite. Accordingly, the skilled artisan cannot make any meaningful deductions pertaining to this study.
Therefore, when all the aforementioned factors are considered *in toto*, it clearly require undue experimentation to practice the claimed invention.

Claim 18 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claim is directed toward a method of enhancing immune responses to an infectious agent by administering low-doses of IL-2 to the subject **prior** to vaccination with a suitable immunogen. The prior art teaches that IL-2 can be an effective adjuvant when administered concomitantly with immunogen or after immunogen administration. However, the art does not support applications involving the administration of IL-2 prior to administration of the immunogen.

The legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230

U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide any evidence demonstrating that IL-2 administration, prior to immunogen administration, is capable of inducing a meaningful immune response. As set forth below, the choice of immunogen, adjuvant, immunization route and schedule, and host immune state are all critical parameters that need to be considered when assessing vaccine and adjuvant efficacy. Morever, the prior art suggests that these factors are critical and the success of any given combination of adjuvant and immunogen can be predicted, but must be determined empirically. However, the disclosure fails to provide any guidance on these subjects.

2) The disclosure fails to provide adequate guidance pertaining to vaccine formulations (i.e., nature and dose of immunogen), immunization schedule, route of administration, and immune status of host being immunized. The prior art teaches that these factors must all be carefully considered before embarking on given immunization protocol (Newman and Powell, 1995).

3) The prior art teaches that cytokine administration prior to immunogen administration may not be effective at inducing strong immunogen-specific immune responses (Barouch *et al.*, 1998; Gursel *et al.*, 1998). Barouch and colleagues reported that maximal immune responses are obtained when the immune system is first primed with

the immunogen of choice, followed by cytokine amplification. Gursel and coworkers noted that IL-2 augments immune responses only when coadministered with the immunogen. Thus, these teachings all contradict applicant's assertion the IL-2 administration prior to vaccination would be effective.

4) The disclosure fails to provide any working embodiments demonstrating that low-dose IL-2 administration, before vaccine administration, augments the immune response to the immunogen of interest. As noted supra, the prior art suggests that IL-2 augments immune responses when coadministered with immunogen or administered after the immune system is first primed with immunogen. Thus, it does not appear that administration of low-dose IL-2 prior to vaccination would have the intended result. Accordingly, applicants would be expected to provide suitable working examples with a reasonable number of immunogens and vaccination regimens.

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation to practice the claimed invention.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 9:30 AM to 7:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, Laurie Scheiner or James Housel, can be reached at (571) 272-0910 or (571) 272-0902, respectively. Direct general inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Formal communications may be submitted through the official facsimile number which is (703) 872-9306. Hand-carried formal communications should be directed toward the customer window located in Crystal Plaza Two, 2011 South Clark Place, Arlington, VA. Applicants are directed toward the O.G. Notice for further

guidance. 1280 O.G. 681. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

24 July, 2004